



## General

### Guideline Title

Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* genotype and use of ondansetron and tropisetron.

### Bibliographic Source(s)

Bell GC, Caudle KE, Whirl-Carrillo M, Gordon RJ, Hikino K, Prows CA, Gaedigk A, Agundez JAG, Sadhasivam S, Klein TE, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther. 2017 Aug;102(2):213-8. [30 references] [PubMed](#)

### Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report [Clinical Practice Guidelines We Can Trust](#).

■■■■= Poor ■■■= Fair ■■■= Good ■■■= Very Good ■■■= Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
■■■■	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group

UNKNOWN	Methodologist Involvement
■□□□□	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
■■■■■	Search Strategy
■■■■■	Study Selection
■■■■■	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
■■■■■	Grading the Quality or Strength of Evidence
■■■■■	Benefits and Harms of Recommendations
■■■■■	Evidence Summary Supporting Recommendations
■■■■■	Rating the Strength of Recommendations
■■■■■	Specific and Unambiguous Articulation of Recommendations
■■□□□	External Review
■■■■■	Updating

## Recommendations

### Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

#### Genetic Test Interpretation

Clinical laboratories rarely sequence through the cytochrome P450 2D6 (*CYP2D6*) gene or interrogate every known variant position. Instead, they typically test for variants that are used to determine high frequency allele haplotypes using the star-allele (\*) nomenclature system, found at The Human Cytochrome P450 (CYP) Allele Nomenclature Database (<http://www.cypalleles.ki.se> ). Supplementary Table S1 (see the "Availability of Companion Documents" field) and tables found on the [PharmGKB Web site](#)  contains a list of *CYP2D6* alleles, the specific combination of variants that can be used to determine the allele, functional status, and frequency across major ethnic populations, as reported in the literature.

Genetic test results are reported as diplotypes, or the combination of the maternal and paternal alleles (e.g., *CYP2D6*\*1/\*2). Phenotypes are assigned based on the reported *CYP2D6* diplotype, as summarized in Table 1, below.

The limitations of genetic testing as described here include: (1) rare variants are often not detected; (2) known star (\*) alleles not tested for will not be reported, and, instead, the patient will be reported as a

\*1; and (3) tests are not designed to detect unknown or *de novo* variants. The Supplementary Data ("Genetic Test Interpretation" section) contains additional information regarding *CYP2D6* genetic test interpretation and phenotype assignment.

#### Available Genetic Test Options

See Supplementary Material and [www.ncbi.nlm.nih.gov/gtr/](http://www.ncbi.nlm.nih.gov/gtr/)  for more information on commercially available clinical testing options.

#### Incidental Findings

Currently, there are no diseases or conditions consistently linked to the variation in the *CYP2D6* gene independent of drug metabolism and response.

#### Other Considerations

Not applicable

Table 1. Assignment of Likely *CYP2D6* Phenotypes Based on Diplotypes

Likely Phenotype	Activity Score	Genotypes <sup>a</sup>	Examples of <i>CYP2D6</i> Diplotypes
<i>CYP2D6</i> ultrarapid metabolizer (~1%-2% of patients) <sup>b</sup>	>2.0	An individual carrying duplications of functional alleles	*1/*1xN, *1/*2xN, *2/*2xN <sup>c</sup>
<i>CYP2D6</i> normal metabolizer (~77%-92% of patients)	2.0-1.0 <sup>d</sup>	An individual carrying two normal function alleles or two decreased function alleles or one normal and no function allele or one normal function and one decreased function allele or combinations of duplicated alleles that result in an activity score of 1.0-2.0.	*1/*1, *1/*2, *1/*4, *1/*5, *1/*9, *1/*41, *2/*2, *41/*41
<i>CYP2D6</i> intermediate metabolizer (~2%-11% of patients)	0.5	An individual carrying one decreased function and one no function allele	*4/*10, *4/*41, *5/*9
<i>CYP2D6</i> poor metabolizer (~5%-10% of patients)	0	An individual carrying only no functional alleles	*3/*4, *4/*4, *5/*5, *5/*6

<sup>a</sup>Assignment of allele function and citations for allele function can be found in the *CYP2D6* Allele Definition Table and *CYP2D6* Allele Functionality References Table 1 (see the "Availability of Companion Documents" field).

<sup>b</sup>See the *CYP2D6* Frequency Table 1 (see the "Availability of Companion Documents" field) for race-specific allele and phenotype frequencies or see Gaedigk et al.

<sup>c</sup>Where xN represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see Supplementary Data for additional information on how to translate diplotypes into phenotypes.

<sup>d</sup>Patients with an activity score of 1.0 may be classified as intermediate metabolizers (IMs) by some reference laboratories.

#### Dosage Recommendations/Therapeutic Recommendations

Table 2, below, summarizes the therapeutic recommendations for ondansetron and tropisetron based on *CYP2D6* phenotype. Gene duplication has been shown to be associated with higher metabolism and clearance of ondansetron resulting in lower area under the plasma concentration-time curve. This translates clinically into a decreased response to ondansetron and tropisetron, specifically increased risk of vomiting in *CYP2D6* ultrarapid metabolizers (UMs). If the *CYP2D6* genotype is known, alternative 5-HT<sub>3</sub>

receptor antagonist antiemetics not metabolized by CYP2D6 (e.g., granisetron) should be considered in CYP2D6 UMs. Although dolasetron, palonosetron, and ramosetron are also metabolized by CYP2D6 (Supplementary Table S3), limited evidence is available regarding the utilization of *CYP2D6* genetic variation to guide use of these drugs.

The strength of this recommendation is based on the evidence provided in Supplementary Table S2 and the availability of suitable antiemetics not metabolized by CYP2D6. Currently, there are limited published data to support a recommendation in CYP2D6 IMs and poor metabolizers (PMs). Of note, the prescribing information for intravenous (i.v.) Zofran states, based on unpublished data, that the pharmacokinetics of i.v. ondansetron did not differ between CYP2D6 PMs and CYP2D6 normal metabolizers (NMs).

At the time of this writing, there are no data available on CYP2D6 genotype's effect on ondansetron or tropisetron response in the pediatric patient populations, although there is no reason to suspect that *CYP2D6* genetic variation will affect this drug's metabolism differently in children compared with adults. Because CYP2D6 catalytic activity in neonates (<1 month old) depends strongly on developmental aspects, the impact of CYP2D6 in this patient population might be different than adults or older children.

Table 2. Dosing Recommendations for Ondansetron and Tropisetron Based on *CYP2D6* Genotype

Phenotype	Implication	Therapeutic Recommendation	Classification of Recommendation	Consideration for Alternative 5-HT <sub>3</sub> Receptor Antagonists Antiemetics <sup>a</sup>
CYP2D6 ultrarapid metabolizer	Increased metabolism to less active compounds when compared to NMs and is associated with decreased response to ondansetron and tropisetron (i.e., vomiting)	Select alternative drug not predominantly metabolized by CYP2D6 (i.e., granisetron). <sup>b</sup>	Moderate	Dolasetron, palonosetron, and ramosetron are also metabolized by CYP2D6. Limited evidence is available regarding the utilization of <i>CYP2D6</i> genetic variation to guide use of these drugs.
CYP2D6 normal metabolizer	NM	Initiate therapy with recommended starting dose. <sup>b</sup>	Strong	
CYP2D6 intermediate metabolizer	Very limited data available for CYP2D6 IMs	Insufficient evidence demonstrating clinical impact based on <i>CYP2D6</i> genotype. Initiate therapy with recommended starting dose. <sup>b</sup>	No recommendation	
CYP2D6 poor metabolizer	Very limited data available for CYP2D6 PMs	Insufficient evidence demonstrating clinical impact based on <i>CYP2D6</i> genotype. Initiate therapy with recommended starting dose. <sup>b</sup>	No recommendation	

5-HT<sub>3</sub>, 5-hydroxytryptamine type 3; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer

<sup>a</sup>Clinical Pharmacogenetics Implementation Consortium strength of recommendation: no recommendation.

<sup>b</sup>Drug-drug interactions and other patient characteristics (e.g., age, renal function, and liver function) should be considered when selecting alternative therapy.

### Recommendations for Incidental Findings

Not applicable

### Other Considerations

The syndrome of congenital prolongation of the QT interval of the electrocardiogram is associated with a risk of potentially fatal polymorphic ventricular tachycardia, which is commonly referred to as torsades de pointes. Drugs that prolong the QT interval, such as ondansetron, should generally be avoided in patients with this diagnosis, as well as in those patients considered borderline. In September 2011, the U.S. Food and Drug Administration (FDA) issued a safety communication reporting a change to the medication label by adding a warning to avoid ondansetron use in patients with congenital long QT syndrome. The alert also recommended electrocardiogram monitoring for patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or patients taking concomitant medications that prolong the QT interval. In June 2012, the FDA issued another safety communication reporting changes to the ondansetron label regarding i.v. dosing. This alert recommended that no single i.v. dose should exceed 16 mg. The alert noted new evidence suggesting that QT prolongation is dose dependent. Therefore, in patients for whom genetic testing indicates intermediate or poor CYP2D6 metabolism, potentially elevated blood levels of ondansetron would suggest these patients might be at an even greater risk for torsades de pointes even with the 16 mg maximum dose. However, there are no clinical data demonstrating greater QT prolongation in CYP2D6 PMs.

CYP2D6 genetic variants do not account for all variations observed for ondansetron or tropisetron response. In addition to specific patients factors (such as smokers vs. nonsmokers and male vs. female), other genes have been implicated in the response to ondansetron, including the adenosine triphosphate-binding cassette subfamily B member 1 gene (*ABCB1*) and the genes for the serotonin 5-HT<sub>3A</sub> and 5-HT<sub>3B</sub> receptors. Genetic variation in *CYP3A5* has been found to influence concentrations of R-ondansetron; however, to date, there are no data to support how *CYP3A5* variation impacts antiemetic efficacy in individuals taking ondansetron and tropisetron. However, one study has found that variations in *CYP3A5* and *CYP1A1* impact systemic clearance and exposure of granisetron in pregnant women. Additional studies are needed to elucidate the role of variation in these genes in antiemetic therapy.

### Definitions

#### Strength of Therapeutic Recommendations

**Strong:** The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

**Moderate:** There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

**Optional:** The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

**No recommendation:** There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

Chemotherapy-induced, radiation-induced, and postoperative nausea and vomiting

## Guideline Category

Evaluation

Management

Prevention

Treatment

## Clinical Specialty

Medical Genetics

Oncology

Pharmacology

Radiation Oncology

Surgery

## Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

## Guideline Objective(s)

To provide information to allow the interpretation of clinical cytochrome P450 2D6 (*CYP2D6*) genotype tests so that the results can be used to guide use of the 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) receptor antagonists, ondansetron and tropisetron

## Target Population

Patients undergoing chemotherapy, radiotherapy, or anesthesia for surgery

## Interventions and Practices Considered

Use of cytochrome P450 2D6 (*CYP2D6*) genotyping to guide use of the 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) receptor antagonists, ondansetron and tropisetron

## Major Outcomes Considered

Effect of cytochrome P450 2D6 (*CYP2D6*) on 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) receptor antagonists, ondansetron and tropisetron clinical outcomes or effect on 5-HT<sub>3</sub> receptor antagonist pharmacokinetic parameters

## Methodology

### Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

#### Retrieval of the Evidence Linking Genotype to Drug Variability

The PharmGKB Scientific Curator, the Clinical Pharmacogenetics Implementation Consortium (CPIC) coordinator or authors with experience in literature or systematic review conduct the literature review and present the results to the writing committee. A search of PubMed and OVID MEDLINE is performed using the keywords for the gene and drug of interest, for example: (gene name) OR (gene symbol) OR (dbSNP rs number) OR (gene common names) AND (drug name OR drug class name). Furthermore, papers listed on PharmGKB are cross-checked as there may be annotations for the papers and/or additional publications. Where available, evidence evaluating the outcomes when prescribing has been altered based on genetic testing is included. For most gene-drug pairs, randomized controlled trials comparing clinical outcomes with genotype-guided dosing versus conventional dosing are not available.

#### Literature Review

The authors searched the PubMed® database (1966 to September 2015) for the following keywords: (cytochrome P450 2D6 or *CYP2D6*) AND (ondansetron, granisetron, tropisetron, palonosetron, ramosetron, 5-HT<sub>3</sub> receptor antagonists). Using these search terms, 43 publications were identified. In addition, studies annotated in PharmGKB (<http://www.pharmgkb.org> ) were identified. Study inclusion criteria included publications that included analyses for the association between *CYP2D6* genotypes and metabolism of 5-hydroxytryptamine type 3 antagonists (5-HT<sub>3</sub>) or 5-HT<sub>3</sub> antagonist-related adverse drug events or clinical outcomes. Non-English manuscripts were excluded.

The *CYP2D6* allele frequency tables (see the "Availability of Companion Documents" field) are updates of those previously published in CPIC guidelines. Updates to the *CYP2D6* allele frequency tables were made by searching the PubMed® database (1995 to July 2016). The following criteria were used for *CYP2D6*: (*CYP2D6* or 2D6 or cytochrome P4502D6) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity) with filter limits set to retrieve "full-text" and "English" literature. In addition, reports were also identified from citations by others or review articles. Studies were considered for inclusion in the *CYP2D6* frequency table if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or genotype frequencies were reported, (3) the method by which the genes were genotyped was indicated, (4) the sample population consisted of at least 50 individuals with a few exceptions (e.g., smaller cohorts that were part of larger studies) and (5) the study represented an original publication (no reviews or meta-analyses).

## Number of Source Documents

Following application of the inclusion criteria, 7 publications were reviewed and included in the evidence table (Supplemental Table S2 [see the "Availability of Companion Documents" field]).

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

### Levels of Evidence Linking Genotype to Phenotype

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

## Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: *in vivo* pharmacokinetic and pharmacodynamic data, *in vitro* enzyme activity of tissues expressing wild-type or variant-containing CYP2D6, *in vitro* CYP2D6 enzyme activity from tissues isolated from individuals of known CYP2D6 genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

### Summarization and Presentation of the Evidence Linking Genotype to Drug Variability

Publications supporting a major finding are usually considered as a group and scored by members of the writing committee based on the totality of the evidence supporting that major finding. Thus, it is possible for an evidentiary conclusion based on many papers, each of which may be relatively weak, to be graded as "moderate" or even "strong," if there are multiple small case reports or studies that are all supportive with no contradictory studies. The rating scheme (see the "Rating Scheme for the Strength of the Evidence" field) uses a scale modified slightly from Valdes et al. Primary publications are summarized in the Evidence Table which is published in the manuscript supplemental material (see the "Availability of Companion Documents" field). It is the writing committee's evaluation of this evidence that provides the basis for the therapeutic recommendation(s).

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

## Identification of Content Experts and Formation of Writing Committee

Once a guideline topic has been approved by Clinical Pharmacogenetics Implementation Consortium (CPIC) members and the Steering Committee, a senior author is identified through self-nomination or by request of the CPIC Steering Committee. The senior author takes responsibility for forming the writing committee and completing the guideline. The writing committee is multidisciplinary, comprising a variety of scientists, pharmacologists, and clinicians (e.g., pharmacists and physicians). Authors will have a track record of publication and/or expertise in the specific topic area of the guideline. PharmGKB assigns at least one Scientific Curator to each CPIC guideline writing committee who has expertise in searching, compiling and evaluating the evidence for gene-drug associations, and making it computable and available on the PharmGKB Web site. Furthermore, PharmGKB curators often take primary responsibility for completing background gene and drug summaries, assigning likely phenotypes based on genotypes (i.e., "Table 1" in guidelines), literature review, as well as preparing supplementary material provided in each guideline (i.e., genotypes that constitute the star (\*) alleles or haplotypes, frequencies of alleles in major race/ethnic groups, genetic test interpretation and availability, and evidence linking genotype with phenotype).

## Development of Therapeutic Recommendation and Assignment of Strength of the Recommendation

The writing committee discusses the evaluation of the literature and develops a draft recommendation via Web conferences and email communication. CPIC's therapeutic recommendations are based on weighing the evidence summarized in the supplementary Evidence Table from a combination of preclinical functional and clinical data, as well as on any existing consensus guidelines. Evidence related to the suitability of alternative medications or dosing that may be used based on genetics must be weighed in assigning the strength of the recommendation. Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians and are presented in the Table 2 of each guideline and occasionally in an algorithm.

To assign strength to a recommendation, CPIC uses a transparent three category system (see the "Rating Scheme for the Strength of the Recommendations" field) for rating recommendations that was adopted with slight modification from the rating scale for evidence-based recommendations on the use of antiretroviral agents (<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf> ). Each recommendation also includes an assessment of its usefulness in pediatric patients.

CPIC guidelines currently focus on gene-drug pairs for which at least one of the prescribing recommendations is actionable (e.g., recommendation to alter a dose or consider an alternative drug based on the genotype-phenotype relationship). For these and many other gene-drug pairs, PharmGKB also contains clinical annotations that are genotype-based summaries of the association between a drug and a particular variant. Each clinical annotation is assigned a level of evidence depending on population, replication, effect size and statistical significance.

Refer to "Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process" (see the "Availability of Companion Documents" field) for additional information.

## Rating Scheme for the Strength of the Recommendations

### Strength of Therapeutic Recommendations

**Strong:** The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

**Moderate:** There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

**Optional:** The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

## Cost Analysis

Analyses of cost-effectiveness are beyond the scope of the guideline.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

### Internal and External Review, Comment, and Approval Process

Once the writing committee has completed and approved a draft guideline, the draft guideline is circulated to the Clinical Pharmacogenetics Implementation Consortium (CPIC) co-leaders and coordinator for content review. The guideline is reviewed for compliance with the CPIC Standard Operating Procedures and required format. The guideline draft is then discussed on a CPIC conference call with all CPIC members and circulated to the members for further review and approval. At each stage, feedback is considered for incorporation into the guideline and/or revision of the guideline, as supported by the available evidence and expert clinical judgment of the senior author and writing committee. Finally, the guideline manuscript undergoes typical external scientific peer review by the journal prior to publication. Current agreements with the American Society for *Clinical Pharmacology and Therapeutics* give the journal *Clinical Pharmacology and Therapeutics* the first right of refusal for publication of CPIC guidelines; as part of this agreement, the guidelines are freely posted to PharmGKB immediately upon publication. In general *Clinical Pharmacology and Therapeutics* uses a minimum of two external expert peer-reviewers and an editorial board member with content expertise as reviewers for each CPIC guideline.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The evidence summarized in Supplemental Table S2 (see the "Availability of Companion Documents" field) is graded on a scale of high, moderate, and weak, based upon the level of evidence (see the Rating Scheme for the Strength of the Evidence" field). Every effort was made to present evidence from high-quality studies.

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

The potential benefit of using cytochrome P450 2D6 (*CYP2D6*) genotype to guide ondansetron and tropisetron use is that patients with genotypes that are associated with a decreased response (e.g., *CYP2D6* ultrarapid metabolizers [UMs]) may be identified and alternative antiemetics administered.

## Potential Harms

- As with any laboratory test, a possible risk to patients is an error in genotyping or phenotype prediction, along with the presence of a rare genomic variant not tested for, which could have long-term adverse health implications for patients.
- Mild headache, constipation, and transient elevations in liver enzymes are common side effects of 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) receptor antagonists. Ondansetron has also been associated with cardiac adverse events such as corrected QT prolongation.

## Contraindications

### Contraindications

Drugs that prolong the QT interval, such as ondansetron, should generally be avoided in patients with this diagnosis, as well as in those patients considered borderline.

## Qualifying Statements

### Qualifying Statements

At this time, the evidence does not justify increasing the dose in cytochrome P450 2D6 (*CYP2D6*) ultrarapid metabolizers (UMs) because dose adjustments based on *CYP2D6* UMs have not been studied and a detailed recommendation of dosing for the different *CYP2D6* phenotypes is missing. Additionally, there is a single intravenous (i.v.) dose maximum of 16 mg in the U.S. Food and Drug Administration (FDA) labeling that might prevent increases in dosing in certain situations. *CYP2D6* genotyping is reliable when performed in qualified laboratories (e.g., Clinical Laboratory Improvement Amendments [CLIA]-certified).

#### Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

Rare *CYP2D6* variants may not be included in the genotype test used and patients with rare variants may be assigned a "wild-type" (*CYP2D6\*1*) genotype by default. Thus, an assigned "wild-type" allele could potentially harbor a no or decreased function variant. Furthermore, it is important that the genetic testing platform include testing for gene copy number to identify *CYP2D6* UMs. Caution should be used regarding molecular diagnostics of *CYP2D6* gene copy-number variation because commercially available genotyping results may differ between diagnostic laboratories depending on assay design. Like all diagnostic tests, *CYP2D6* genotype is one of multiple pieces of information that clinicians should consider when making their therapeutic choice for each patient. Furthermore, several other factors cause potential uncertainty in the genotyping results and phenotype predictions. These are discussed in detail in the Supplementary Data (see the "Availability of Companion Documents" field).

#### Disclaimer

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision-making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health care provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and

the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

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#### Underlying Assumption

The key underlying assumption for all CPIC guidelines is that clinical high-throughput and pre-emptive genotyping will eventually become common practice and clinicians will increasingly have patients' genotypes available before a prescription is written. Therefore, CPIC guidelines are designed to provide guidance to clinicians as to how available genetic test results should be interpreted to ultimately improve drug therapy, rather than to provide guidance as to whether a genetic test should or should not be ordered.

## Implementation of the Guideline

### Description of Implementation Strategy

#### Implementation Resources for This Guideline

The guideline supplement (see the "Availability of Companion Documents" field) contains resources that can be used within EHRs to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see the "Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support" section of the Supplementary Material). Clinical implementation resources include cross-references for drug and gene names to widely used terminologies and standardized nomenclature systems, workflow diagrams, a table that translates genotype test results into a predicted phenotype with genetic test interpretation, and example text for documentation in the electronic health record and point-of-care alerts.

Refer to "Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process" (see the "Availability of Companion Documents" field) for information on guideline dissemination and connecting the guidelines to practice.

### Implementation Tools

#### Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

Staying Healthy

### IOM Domain

Effectiveness

Patient-centeredness

## Identifying Information and Availability

### Bibliographic Source(s)

Bell GC, Caudle KE, Whirl-Carrillo M, Gordon RJ, Hikino K, Prows CA, Gaedigk A, Agundez JAG, Sadhasivam S, Klein TE, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. Clin Pharmacol Ther. 2017 Aug;102(2):213-8. [30 references] [PubMed](#)

### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

2017 Aug

### Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

### Source(s) of Funding

This work was funded by the National Institutes of Health (NIH) for the Clinical Pharmacogenetics Implementation Consortium (CPIC) (R24GM115264) and PharmGKB (R24GM61374), RO1 GM008076-05 (A.G.).

### Guideline Committee

The Writing Committee

### Composition of Group That Authored the Guideline

*Authors:* GC Bell, Personalized Medicine Program, Mission Health, Asheville, North Carolina, USA; KE Caudle, Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; M Whirl-Carrillo, Department of Genetics, Stanford University, Stanford, California, USA; RJ Gordon, University of California, San Diego, Department of Anesthesiology, San Diego, California, USA; K Hikino, Committee on Clinical Pharmacology and Pharmacogenomics, University of Chicago, Chicago, Illinois, USA; CA Prows, Division of Human Genetics, Division of Patient Services, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; A Gaedigk, Division of Clinical Pharmacology, Toxicology, and Therapeutic Innovation, Children's Mercy–Kansas City, Kansas City, Missouri, USA; JAG Agundez, Department of Pediatrics, University of Missouri–Kansas City, Kansas City, Missouri, USA, and Department of Pharmacology, University of Extremadura, Cáceres, Spain; S Sadhasivam, Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, Ohio, USA, and Department of Anesthesia, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; TE Klein, Department of Genetics,

Stanford University, Stanford, California, USA; M Schwab, Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany, and University of Tübingen, Germany, Department of Clinical Pharmacology, University Hospital Tübingen, Tübingen, Germany, and Department of Pharmacy and Biochemistry, University of Tübingen, Tübingen, Germany

## Financial Disclosures/Conflicts of Interest

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### Conflict of Interest

T.E.K. and M.W.C. are paid scientific advisors to the Rxight Pharmacogenetic Program. A.G. and R.G. are paid consultants for Millennium Health, LCC. All other authors declare no conflicts of interest. J.A.G.A. acknowledges financial support from RD12/0013/0002; ISCIII and FEDER.

### Management of Conflicts of Interest

All authors must declare any funding interests and activities potentially resulting in conflict of interest by written disclosure to the Clinical Pharmacogenetics Implementation Consortium (CPIC) Steering Committee and writing committee before the approval of the authorship plan. Included are all possible conflicts including spouses/family members in declarations, National Institutes of Health (NIH) funding that could be interpreted to indicate that authors are "advocates" of the recommendations, as well as any sources of revenue from consulting, patents, stock ownership, etc. All conflicts of interest are reported in the guideline manuscript.

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Available from the [Clinical Pharmacogenetics Implementation Consortium \(CPIC\) Web site](#)

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## Availability of Companion Documents

The following are available:

Supplementary material, including tables and methodological information, is available from the [Clinical Pharmacogenetics Implementation Consortium \(CPIC\) Web site](#) .

A variety of resources, including definition, frequency, functionality, and diplotype-phenotype tables; drug mapping; gene resource mapping; and clinical decision support, are available from the [CPIC Web site](#) .

Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. *Curr Drug Metab.* 2014;15(2):209-17. Available from the [CPIC Web site](#)

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## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on September 14, 2017. The information was verified by the guideline developer on October 30, 2017.

This NEATS assessment was completed by ECRI Institute on August 31, 2017. The information was verified by the guideline developer on October 30, 2017.

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